PRECOCIOUS PUBERTY : CLINICAL AND ENDOCRINE PROFILE AND PREDICTORS OF NEUROGENIC ETIOLOGY IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY

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CERTIFICATE

This is to certify that the dissertation entitled, "**SEXUAL PRECOCITY: CLINICAL AND ENDOCRINE PROFILE AND PREDICTORS OF NEUROGENIC ETIOLOGY IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY"** submitted by **DR.P.SRINIVASAN** to the Faculty of Paediatrics, The Tamilnadu Dr.M.G.R Medical University, Chennai, in partial fulfilment of the requirements for the award of M.D. Degree (Paediatrics) is a bonafide research work carried out by him under our direct supervision and guidance, during the academic year 2009-2012.

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I, **DR. P.SRINIVASAN**, solemnly declare that the dissertation titled **"SEXUAL PRECOCITY: CLINICAL AND ENDOCRINE PROFILE AND PREDICTORS OF NEUROGENIC ETIOLOGY IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY"** has been prepared by me under the expert guidance and supervision of **Prof.Dr.S.SUNDARI, M.D, D.C.H.,** Additional Professor, Institute of child health and hospital for children, Madras Medical College, Chennai – 3. This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of M.D. Degree Examination in Paediatrics (Branch VII).

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CONTENTS

INTRODUCTION

Puberty is characterized by the appearance of secondary sexual features and transition from the sexually immature form to the sexually mature form. Precocious precocity is defined as the appearance of secondary sexual characteristics in an age that is less than 2-2.5 standard deviation below the mean age of puberty for general population (1, 2) or the onset of menstruation before 9.5 years in girls (3). Puberty sets in with activation of the hypothalamic-pituitary-gonadal (HPG axis). The hypothalamic-pituitary-gonadal (HPG) axis is relatively quiescent during childhood, under higher inhibitory influences that still remain incompletely understood. Any disruption to this normal inhibition of the HPG axis during childhood results in “gonadotropin dependent or central or true precocious puberty”. Abnormal secretion or exposure to sex steroids independent of the HPG axis results in “gonadotropin independent or pseudo or peripheral precocious puberty".

True precocious puberty is always isosexual and the physical signs of sexual development are in keeping with the phenotypic gender of the child. In precocious pseudo puberty, the sex characteristics may be "isosexual" or "heterosexual". Precocious pseudo puberty may induce maturation of the hypothamic - pituitary - gonadal axis and trigger the onset of true sexual precocity.

Incomplete sexual precocity or variants of pubertal developments refers to those disorders in which pubertal development is mild or non progressive resulting in premature thelarche or premature adrenarche or premature menarche.

Normal pubertal development

Pubertal development coincides with the activation and maturation of the HPG axis and also with the maturation of the adrenal cortex. The maturation of the HPG axis is responsible for testicular enlargement and increase in penile size in boys, and breast development and menarche in girls. The increased androgen production from the adrenal cortex is responsible for development of pubic hair, body odour and acne.

Pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalamus marks the onset of puberty. GnRH release is regulated by the hypothalamic peptide hormone kisspeptin and its receptor GPR54 (a G protein coupled receptor 54) (3). The expression of KISS-1 mRNA and GPR54 receptor correlates with the onset of puberty. The identification of activating GPR54 mutation as a cause of precocious puberty has strengthened the role of kisspeptin in pubertal regulation (4). GnRH stimulates the anterior pituitary to secrete luteinising hormone (LH) and follicle stimulating hormone (FSH). LH and FSH enter the systemic circulation and stimulate the ovaries and testes to produce

estrogen and testosterone respectively. These sex steroids exert a complex feedback on GnRH and gonadotropin release.

Maturation of the adrenal cortex (adrenarche) leads to production of increased adrenal androgens which are responsible for many of the secondary sexual characteristics like pubic hair (pubarche), body odour and acne. Adrenarche is a gradual process and may precede central puberty.

Physical changes occurring during puberty (secondary sexual characteristics) are a result of GnRH – driven sex steroids (estrogen and testosterone) and the adrenal androgens. The first sign of central puberty in boys is testicular enlargement (4ml) and in girls is breast development. Pubic hair may precede breast development in many girls. The sequence of progression of sexual development in both boys and girls has been well described by Tanner staging or sexual maturity staging (SMR) (5, 6). The growth spurt occurring during puberty is the result of increased sex hormones and growth hormone secretion. In boys the peak growth velocity occurs in midpuberty, whereas in girls it occurs with the onset of puberty. Maturation of the epiphyseal plates and accrual of bone mineral density also occurs during puberty and is dependent on estrogen.

Timing of puberty is dependent on genetic, psychosocial and environmental factors. Many studies have demonstrated that black girls enter puberty earlier than white girls (7). Environmental factors like

nutrition also play a role in the timing of puberty, with obese girls entering puberty much earlier (8).

The standards for pubertal timing as demonstrated by observational studies by Tanner and Marshall (5, 6) were between 9.5 years and 13 years with mean of 11.6 years in males as evidenced by enlargement of testes. In females the age of pubertal onset was between 8.5 – 13 years with mean age of 11.2 years as evidenced by breast enlargement.

Hormonal changes in puberty:

Sex hormone levels are high at birth and remain so during infancy due to high gonadotropin levels (minipuberty).high estrogen levels in girls at birth reflect transplacental transfer of maternal estrogen. This may result in transient breast enlargement, galactorrhea and withdrawal vaginal bleeding. Minipuberty is more marked in boys and may last upto one year of life (9). Beyond infancy, gonadotropin levels become undetectable till the onset of puberty. However; the prepubertal phase is not quiescent and is characterized by episodic secretion of gonadotropin. Baseline FSH levels are higher compared to LH in Prepubertal girls and may overlap with those observed in pubertal girls. Increased GnRH secretion is the first identifiable event of puberty. This is related to the increased production of hypothalamic kisspeptin in response to central (neurotransmitters) and peripheral signals (leptin and ghrelin).during the initial phases of puberty, GnRH pulses occur during night followed by

pulses during both day and night. This results in increase in the LH levels as much as 25 times during puberty as compared to FSH, which increases only 2.5 fold (9). LH levels are, therefore better indicators of pubertal status compared to FSH levels. The pulsatile pattern disappears after completion of pubertal changes.

Pubertal development in girls:

Enlargement of breast (thelarche) is the first pubertal event in girls closely followed by the development of pubic hair (pubarche) and onset of menstrual cycles (menarche). Breast development may remain unilateral initially or may be asymmetrical to begin with during the first year of thelarche. Although pubarche occurs within six months of thelarche it may precede thelarche in 10% girls (9). Menarche is usually attained within two years of thelarche; menstrual cycles are usually anovulatory during the first year.

Puberty is associated with increase in vaginal length and appearance of estrogenic changes in the vaginal mucosa. Inspection of vaginal mucosa helps in assessing the pubertal status of a girl. Red glistening vaginal mucosa suggests lack of estrogen exposure and prepubertal state, while pink mucosa with mucus production is indicative of pubertal state and estrogenic effect. The first radiologically identifiable change of puberty is the increase in the ratio of uterine fundus to cervix, resulting in change in the shape of uterus from a tubular structure to a

pear shaped one (9). This is followed by increase in uterine length and endometrial thickness. Endometrial thickness greater than 5mm suggests imminent menarche. Puberty is associated with increase in ovarian volume and development of multiple ovarian follicles giving the appearance of multicystic ovary. It can be readily differentiated from polycystic ovarian syndrome (PCOS) by the presence of small (<8 mm) and centrally located cysts.

Estrogen accelerates growth by direct effect on the growth plate and indirect effect on the GH-IGF-1 axis. This results in a pubertal growth spurt with a peak growth velocity of 8-10 cm an year during the first half of puberty (Tanner stage I and II).the extent of growth after puberty may be influenced by the timing of menarche. While most girls grow by 4-6cm after menarche, postmenarchal growth might be 10 cm in girls with early menarche (9). Puberty is associated with change in the amount (increase) and distribution of adipose tissue (feminine distribution).attainment of peak bone mass closely follows peak height velocity and usually occurs by 16 years of age.

The progression of puberty in girls is graded according to Tanner staging, which takes breast and pubic hair development into consideration.

MARSHALL WA AND TANNER JM STAGES OF PUBERTAL DEVELOPMENT IN GIRLS (6).

BREAST DEVELOPMENT

Stage:	Characteristics
I	Prepubertal; elevation of the papilla only
II	Breast buds are noted or palpable; enlargement of the areola
III	Further enlargement of the breast and areola, with no separation of their contours.
IV	Projection of areola and papilla to form a secondary mound above the level of the breast.
V	Adult contour breast with projection of papilla only.

PUBIC HAIR DEVELOPMENT

Stage:	Characteristics
I	Prepubertal; no pubic hair
II	Sparse growth of long, straight or slightly curly, minimally pigmented hair, mainly on the labia.
III	Considerably darker and coarser hair spreading over the mons pubis.
IV	Thick, adult type hair that does not yet spread to the medial surface of thighs
V	Hair adult in type and distributed in the classic inverse triangle.

Pattern of Pubertal Development in Boys

The physical characteristics of the stages of genital and pubic hair development in boys are primarily the result of androgen secretion by the testes. Adrenal androgens may account for some pubic hair development or, in rare cases, even phallic growth. Boys normally enter puberty between the ages of 9 and 14 years (5). Pubertal development in about 98% of normal boys begins with testicular enlargement and is followed within 6 months by the appearance of pubic hair. Boys complete puberty in 2 - 4.5 years (5). Phallic enlargement usually occurs 12 to 18 months after testicular enlargement. The development of axillary and facial hair is highly variable. Axillary hair usually appears 2 years after pubic hair, in stage IV, and facial hairs simultaneously with or slightly after axillary hair.

Pubertal growth spurt in boys occurs later than in girls (Tanner stage III and IV) and is associated with higher peak growth velocity (10-12 cm/year).puberty is associated with decrease in body fat and increase in lean body mass and muscle mass. Boys tend to accrue bone mineral content till the age of 18 years.

Pubertal development in boys is staged according to Tanner’s method.

MARSHALL WA, TANNER JM STAGES OF PUBERTAL DEVELOPMENT IN BOYS (5).

GENITAL DEVELOPMENT

Stage	Characteristics
I	Prepubertal; testicular length < 2.5 cm or volume 1-3 mL
II	Testes > 2.5 cm in the longest diameter or volume 4-8 mL; early penile growth and scrotal growth; scrotal skin is thin, red and rugose
III	testes enlarge (length 3.3-4 cm; volume 10-15 mL); increased penile length and width; and scrotal growth
IV	Penis further enlarged; testes length4-4.5 cm or volume 15-20 mL, with darker scrotal skin color.
V	Genitalia adult in size and shape. Testes >4.5 cm or volume 25 mL

PUBIC HAIR DEVELOPMENT

Stage :	Characteristics
I	Prepubertal, no pubic hair
II	Sparse growth of slightly pigmented, slightly curly pubic hair, mainly at the base of the penis.
III	Thicker, Curlier hair, spread to the mons pubis
IV	Adult type hair that does not yet spread to the medial thighs
V	Adult type hair spread to the medial thighs

Variations of normal pubertal development:

Variations of normal pubertal development like premature thelarche and premature adrenarche can occur in otherwise healthy children and may mimic precocious puberty. These conditions do not require any treatment other than reassurance and follow-up every 3 – 6 months. However, it is important to distinguish these conditions from pathological precocious puberty.

Premature thelarche:

Premature thelarche is characterized by isolated breast enlargement in girls younger than 8 years of age. This condition is self-limited and is not associated with height acceleration or advancement of bone age. Premature thelarche may be unilateral or bilateral and regression may happen when it occurs in girls less than 2 years of age. There may be a mild rise in estradiol levels. GnRH stimulation test demonstrates an increased FSH response with prepubertal LH response. This condition requires no treatment, but mandates close follow-up to ensure that there is no rapid progression to CPP (10).

Premature adrenarche:

Girls are more frequently affected than boys and the benign form of premature adrenarche should be differentiated from pathological forms. With benign premature adrenarche the bone age advancement is <

2 years from the chronological age or equivalent to the height age. Serum dehydroepiandrosteronesulfate (DHEAS) and testosterone levels may be elevated for age, but are appropriate for the Tanner stage of pubic hair development (11). There will be no signs of gonadal maturation in boys or girls. The presence of clitoral hypertrophy or hirsuitism in girls suggests pathological adrenarche. No treatment is necessary for the benign form of premature adrenarche, but close follow-up for abnormal pubertal progression is important. Girls with premature adrenarche have an increased risk for hyperinsulinism and ovarian hyperandrogenism later in life.

Precocious puberty

Precocious puberty is defined as the onset of puberty at a younger age than expected for normal population. Based on Tanner's and Marshal's observational studies (5, 6), pubertal signs occurring prior to 8 years in girls and prior to 9 years in boys are considered precocious. Recent data however have shown a secular trend in the timing of puberty with many girls attaining puberty earlier (12) and thereby opening a debate as to whether the age of onset of normal puberty should be reduced to 7 years in girls.

Central precocious puberty:

Children with central precocious puberty (CPP) exhibit isosexual pubertal development at an early age due to premature activation of the HPG axis. The pubertal stages in CPP are similar to normal puberty but may progress more rapidly. Idiopathic CPP is more common in girls (13) whereas boys with CPP are more likely to have underlying central nervous system (CNS) lesion.CNS mass lesions or malformations are a common cause of CPP (14) especially in boys. Risk factors for a CNS lesion include a younger age and male gender.

In girls, breast development and estrogenisation of vaginal mucosa are the first signs of puberty. Pubarche happens next and if untreated is followed by menarche. Boys have testicular enlargement followed by increased penile size, pubarche, increased muscle mass and deepening of voice. Along with pubertal progression, growth acceleration with significant advancement of bone age occurs. Neurological symptoms like headache, visual disturbances and seizures raise the suspicion of a CNS lesion. Gelastic seizures, which manifest as laughing spells, are characteristic of hypothalamic hamartomas.

Conditions causing GnRH dependent (central or true) precocity (15):

A. Constitutional

B. Idiopathic true precocious puberty

C. CNS tumors

1. Hamartomas of the tuber cinereum
2. Other hypothalamic tumors
    a. Glioma
    b. Astrocytoma
    c. Ependymomas

D. Other CNS disorders

1. Meningitis
2. Encephalitis
3. Granulomas
4. Brain abscesses
5. Suprasellar cysts
6. Hydrocephalus
7. Head trauma

E. Severe Hypothyroidism

F. True precocious puberty after late treatment of congenital virilizing adrenal hyperplasia or other previous chronic exposure to sex steroid.

Peripheral precocious puberty:

Peripheral precocious puberty (PPP) is less common than CPP. It occurs independent of the HPG axis maturation. The HPG axis in peripheral precocious puberty is suppressed by abnormally elevated androgens or estrogens. These sex steroids may originate from the adrenal glands, gonads, other organs or an exogenous source. Estrogen excess induces isosexual precocious puberty in girls and heterosexual puberty in boys; similarly increased androgens induce isosexual precocious puberty in boys and heterosexual puberty in girls.

Peripheral precocious puberty has many different causes. It can be due to external factors like therapeutic or accidental excess of androgens or estrogens. Other causes include sex hormone secreting tumors of the gonads, CNS, adrenals, liver or other organs, defects in steroid biosynthesis or activating mutations of the LH receptors.

Causes of GnRH independent (peripheral or pseudo) precocity (15):

A. McCune - Albright Syndrome (polyostotic fibrous dysplasia)

B. Males (Isosexual)

1. HCG Secreting tumors

    a. CNS tumors (germinoma, chorioepithelioma teratoma)

    b. Hepatoma or hepatoblastoma

2. Excessive androgen Secretion

    a. Congenital adrenal hyperplasia

    b. Virilizing adrenal neoplasm

    c. Leydig cell tumor

    d. Familial gonadotropin independent Leydig cell maturation

C. Males (heterosexual)

1. Adrenal neoplasm (Feminizing)

2. Increased extra glandular conversion of circulating steroids to estrogen

D. Females (Isosexual)

1. Follicular cysts

2. Ovarian tumor

    a. Granulosa cell tumor

    b. Lipoid tumors

    c. Cystadenomas

    d. Ovarian carcinomas

    e. Gonadoblastoma

3. Adrenal tumor

4. Exogenous estrogen

E. Females (Heterosexual)

1. Congenital adrenal hyperplasia

2. Virilizing adrenal neoplasms

3. Virilizing ovarian neoplasms

Diagnostic evaluation of precocious puberty

The diagnostic evaluation of all patients with precocious puberty should begin with a proper and thorough history. The history of age of onset of puberty in other family members is important. History of accidental or iatrogenic exposure to sex steroids should be enquired. History of CNS trauma, infection, presence of neurological symptoms or hypothyroid symptoms will also provide important clues to the diagnosis.

A thorough physical examination should include careful measurement of height, weight, assessment of body proportions and pubertal staging by Tanner or SMR staging. Any evidence of accelerated growth or growth spurt should be recorded. Other secondary sexual features like acne, breaking of voice and body proportions have to be noted. A complete neurological examination including fundoscopy and visual field defects should be done. The physical examination should include signs for specific causes of precocious puberty such as café-au-lait patches or bony lesions of fibrous dysplasia which are commonly seen in McCune Albright syndrome and neurofibromatosis. Any clinical

findings suggestive of hypothyroidism or a palpable thyroid may give a clue to the etiology.

Investigations should be planned based on the probable diagnosis after the history and physical examination. Unnecessary investigations should be avoided if features of precocious puberty are inconsistent or not clearly evident and the patient must be reviewed after a few months for reassessment. A skeletal age assessment is mandatory. The skeletal age in patients with precocious puberty is significantly advanced (> 2 yrs) than their chronological age. The skeletal age can also be used to predict adult height; predicted adult height is an important factor to be considered when planning treatment of precocious puberty.

Initial blood tests should include LH, FSH, and estradiol in girls and testosterone in males. Levels of sex steroid measurements must be done in the morning. DHEAS should be done whenever the patient presents with premature adrenarche. Elevated serum levels of sex steroids (testosterone and estradiol) confirm the diagnosis of precocious puberty but do not differentiate the cause. In girls, estradiol levels are highly variable and have a low sensitivity for diagnosing precocious puberty. Elevated LH and FSH levels point towards CPP. A GnRH stimulation test is very valuable in differentiating CPP from PPP. Peak LH values are used to differentiate pubertal activity of the HPG axis from prepubertal stage. Pre pubertal patients or those with peripheral

precocious puberty have little or no response to GnRH stimulation (16). In boys with prepubertal LH levels, imaging for adrenals and estimation of 17 hydroxyprogesterone (17-OHP) and 11 deoxycortisol (11-OHDOC) should be done. Blood HCG (human chorionic gonadotropin) levels should be estimated if these investigations are non contributory. Testotoxicosis should be considered in boys presenting with peripheral precocity at an early age after exclusion of adrenal pathology or HCG secreting tumour.

Pelvic sonography is a very useful tool in girls to determine the uterine size, uterine corpus: cervix ratio and ovarian size. Tubular uterus with no visible endometrial stripe is suggestive of pre-pubertal state, while pubertal state is characterized by pear shaped structure and endometrial thickness greater than 3mm. The uterus and ovaries are appropriately enlarged in CPP (17). Unilateral enlargement of ovaries may indicate a cyst or tumour as in PPP.

The main aim of evaluation of gonadotropin-dependent precocious puberty is the identification of an underlying organic etiology. High resolution magnetic resonance imaging (MRI) of the hypothalamic-pituitary region is desirable; however, computerized tomography scan may be considered if MRI is not feasible. MRI of the pituitary – hypothalamic region is indicated in all boys and in girls less than 6 years of age with CPP to exclude a CNS lesion (18). MRI may be avoided in

girls with CPP between 6-8 years as the etiology is most often idiopathic CPP. If there are clinical features to suggest an underlying CNS lesion, a MRI scan of the brain should be considered in this age group also.

The diagnostic criteria used for classification according to etiology are presented in (Table 1).

Table 1 : Criteria for diagnosis of central and peripheral precocity

No	Diagnosis	Criteria
1.	Precocious puberty	Secondary sexual characteristics Boys < 9 years Girls< 8 years
2.	Central precocious puberty	High estradiol or testosterone. Precocious puberty LH: FSH pubertal LH: FSH >1 GnRH stimulated LH: FSH >1
3.	Neurogenic central precocious puberty	CPP Known neurological disease Abnormal CT or MRI
4.	Idiopathic central precocious puberty	CPP Normal Neuroimaging
5.	Peripheral precocious puberty	Precocious puberty LH, FSH Prepubertal LH: FSH <1 GnRH stimulated LH: FSH<1
6.	Premature Adrenarche	Pubarche No other secondary sexual features LH, FSH prepubertal DHEA elevated

No	Diagnosis	Criteria
7.	Premature thelarche	Breast enlargement No other secondary sexual features LH, FSH normal
8.	CAH	Premature pubarche/ virilisation Gonads remain prepubertal Elevated 17-OHP, DHEAS, 11deoxycortisol. Hyperplastic adrenals on imaging.
9.	McCune-Albright syndrome	Irregular café-au-lait spots, polyostotic fibrous dsysplasia Elevated estradiol. Multicystic ovaries on USG pelvis Low basal LH & prepubertal response to GnRH stimulation.
10.	Male-limited precocious puberty. (Testotoxicosis)	Virilisation in early childhood. Large testes. Elevated testosterone. Pre-pubertal response to GnRH stimulation.

Management:

Suppression of puberty with GnRH analogues should be considered for CPP when there is significant advancement of skeletal age and at younger age groups as they are at risk of adult short stature due to premature epiphyseal fusion. Girls in the age group 6-8 years with slowly progressive CPP or unsustained CPP may not require treatment, but

GnRH analogs should be considered in the presence of advanced skeletal maturation (height standard deviation score for bone age less than -2) and compromised final height (predicted height below the target height range) (19).

Behavioral problems and psychological stress are also indications for suppression of puberty.

Medical treatment consists of administering drugs which would effectively block gonadotropin release, or interfere with sex steroid synthesis at the gonadal level, or interfere with enzymatic action. Long acting GnRH agonist analogues besides inhibiting gonadotropin release have the additional advantage of inhibiting rapid skeletal maturation and linear growth, which remains unaffected by other forms of therapy. Short-acting GnRH analogues reverse pubertal changes but do not improve auxological outcome. Medroxyprogesterone acetate (MPA) and cyproterone which interfere with sex steroid synthesis, has no beneficial effect on height outcome. Aromatase inhibitor included in the latter category prevents conversion of testosterone to estrogen or blocks the receptors for testosterone and dihydrotestosterone. Long acting GnRH analogues have become the mainstay of treatment in CPP. In general, GnRH analogue therapy has been more successful in boys with CPP.

Discontinuation of treatment:

GnRH analog should be continued till the age of 10 years in girls and 12 years in boys (20). Discontinuation of treatment results in gradual reappearance of secondary sexual characters. Menarche is usually attained around 12-18 months following discontinuation of treatment.

Treatment of peripheral precocious puberty:

Treatment of peripheral precocious puberty should be directed towards correction of the underlying cause (hypothyroidism, ovarian or adrenal tumour). GnRH analogue therapy is ineffective, and the treatment is instead focused on directly inhibiting the synthesis or action of sex steroids. Girls with McCune Albright syndrome are treated with drugs that inhibit the synthesis of estrogen (aromatase inhibitors) such as testolactone. Third generation aromatase inhibitors such as letrozole and anastrozole have been increasingly used.

Most ovarian cysts regress spontaneously and do not require surgical intervention. Patients with complex ovarian cysts (size greater than 8 cm or multiseptate cysts) should undergo estimation of tumour markers (beta-HCG and alpha- fetoprotein) and laparotomy. Thyroid functions should be assessed in all girls with ovarian cysts before performing extensive investigation and surgery (21).

Physiological glucocorticoid therapy is ineffective in retarding the pubertal progress in boys with congenital adrenal hyperplasia. Diagnosis is often delayed in most patients, resulting in gonadotropin-dependent precocious puberty. These children should be treated with GnRH analogs.

In testotoxicosis, combination of anastrozole and anti-androgen biclutamide has shown to be effective (22).

No treatment is required for normal puberty variants like premature thelarche or premature adrenarche. Reassurance and close follow-up to exclude rapid progression to CPP is all that is required for these patients.

Predictors for neurogenic central precocious puberty:

Clinicians who deal with CPP have two main concerns: detection of CNS abnormalities and short final height. The risk for girls with CPP to reach a final height that is too short has been widely debated, and several authors have suggested limiting the use of gonadotropin-releasing hormone analog. Thus, a means of identifying the group of girls who have CPP and are at high risk of CNS abnormalities is essential. In hospital-based studies, CPP revealed CNS abnormalities in 8% to 33% of the girls (23-32). Reported predictors for CNS abnormalities in girls with CPP are young age at the onset of puberty (35, 36, 37) presence of pubic hair at the same time (35) markedly advanced bone age (36, 37) rapid progression of puberty (36, 37) and high plasma gonadotrophins

concentrations (35). Unfortunately, those studies were based on small series with high frequencies of CNS abnormalities suggestive of selection bias (35, 36) or did not include appropriate statistical analysis (37). New recommendations from the Lawson Wilkins Pediatric Endocrine Society (LWPES) (12) and Elders et al (38) were proposed to identify girls who are at high risk (for both CNS abnormalities and short final height), but they were mainly based on a study in which the cause of precocious puberty was not assessed.

Importance of evaluation of children with precocious puberty

1. Identifying children with pathological forms of precocious puberty and differentiating normal variants of pubertal development from the pathological forms.

2. Determining whether the etiology is central (GnRH dependent) or peripheral (GnRH independent). This is crucial to planning appropriate investigations and therapy.

3. The physical growth, body preoccupation and sexual interest correlate with sexual maturity, whereas cognitive advancement, changes in social behavior may correlate more closely with chronologic age. Discordance between chronologic age and sexual maturation increases the stress of adolescence.

4. Early maturing boys enjoy higher self esteem and may seek older companies. They tend to enjoy greater social success. In girls early maturation is associated with poor school performance and lower self esteem.

5. The age of onset of puberty is significant for subsequent growth and final height. Thus with early maturity, child has a paradox of tall stature in childhood but short adult height.

6. The early maturing child often has questions about the somatic and sexual changes they are experiencing which places significant stress on the family.

7. Sexual abuse of the early maturing child.

REVIEW OF LITERATURE

1. **Meena Desai et al.,(23)** from Wadia hospital for children, Bombay studied eighty children (58 girls and 22 boys) with sexual precocity were evaluated clinically and investigated to identify the underlying cause. The mean age of presentation was 4.5 years and the mean age of onset of symptoms was 3.37 years. 72.5% (58) of the girls were classified into five groups : (i) central precocious puberty 50% (29), of which 52% (15) had idiopathic precocious puberty and 48% (14) had neurogenic precocious puberty, (ii) 35% (20) had premature thelarche, (iii) 9% (5) had premature adrenarche, (iv).3.5% (2) had premature menarche and (v) others - Hypothyroidism and McCune Albright syndrome constituted one each. Amongst the 22 boys (27.5%), 50% (11) had central precocious puberty, idiopathic in 27% (3) and neurogenic in 73% (8). The adrenal cause constituted 32% (7), of which 86% (6) were congenital adrenal hyperplasia and 14% (1) were adrenocortical carcinoma. The testicular cause constituted 9% (2). Hypothyroidism and premature adrenarche constituted one each.

2. **Kandhekar et al., (24)** from PGI Chandigarh studied a total of 31 children of which 74.2% (23) were girls and 25.8% (8) were males. 56.5% (13) of the 23 girls had central precocious puberty, of which 85% (11) had idiopathic precocious puberty. Hydrocephalus and hypothyroidism constituted one each. 21.7% (5) had premature

adrenarche and 21.7% (5) had premature thelarche. Out of the 5 premature adrenarche, 60% (3) had congenital adrenal hyperplasia.

75% (6) of the 8 boys had central precocious puberty, of which 66.66% (4) had idiopathic precocious puberty, while hydrocephalus and suprasellar cyst contributed one each. 25% (2) had peripheral precocious puberty contributed by adrenocortical adenoma and virilizing hepatoblastorna.

3. **K.M.Prasanna Kumar et al., (25)** from AIIMS, New Delhi studied Fifteen children (8 boys and 7 girls) with sexual precocity were evaluated. The mean age of onset was 3.5 years in boys and 4.8 years in girls. All the children had growth spurt and most of them were more than 2SD above the mean, for their respective age and sex. 86% (6) of the 7 girls had central precocious puberty, 71.5% (5) contributed by idiopathic precocious puberty and 14.5% (1) contributed by neurogenic cause and 14.5% (1) were premature thelarche. 50% (4) of the boys had central precocious puberty, of which 25% (2) were idiopathic precocious puberty. Hypothalamic hamartoma and hydrocephalus contributed one each. Peripheral cause of precocity was found in 50% (4), all the 4 being congenital adrenal hyperplasia.

4. **Chemaitilly et al., (26)** studied the clinical and laboratory features of 256 patients (26 boys and 230 girls) with CPP. He compared patients with idiopathic CPP (seven boys and 186 girls) to those with

organic CPP, whose pubertal development revealed a central nervous system (CNS) lesion (five boys and 11 girls), and to patients with organic CPP associated with a previously treated CNS lesion (14 boys and 33 girls). Boys with organic CPP, having revealed or treated CNS lesions, started their puberty earlier (3.0 +/- 1.0 years and 6.7 +/- 0.5 years) than boys with idiopathic CPP (8.5 +/- 0.2 years, $P < 0.01$ and < 0.05). Boys with organic CPP associated with a treated CNS lesion had lower luteinizing hormone (LH)/follicle stimulating hormone (FSH) peaks ratio after stimulation with gonadotrophin releasing hormone (GnRH) (1.6 +/- 0.5) than did boys with idiopathic CPP (2.2 +/- 0.3, $P < 0.05$). Girls with organic CPP revealing a CNS lesion started their puberty earlier (3.6 +/- 0.9 years) than girls with idiopathic CPP (6.6 +/- 0.1 years, $P < 0.0$ l) and had higher LH ($P < 0.01$) and FSH peaks (< 0.05). Girls with organic CPP associated with a treated CNS lesion had higher BMI (1.8 +/- 0.2 z-score) than did girls with idiopathic CPP (1.3 +/- 0.1 zs, $P < 0.05$), higher leptin concentrations (11.7 +/- 1.8 microg/l vs. 7.7 +/- 0.5 microg/l, $P <$ 0.0 l), LH peak ($P < 0.01$), FSH peak ($P < 0.05$) and LH/FSH peaks ratio (1 +/- 0.1 vs. 0.8 +/- 0.1, $P < 0.05$). Only 12.4% of the girls with idiopathic CPP had BMI-zs < 0, and their plasma leptins were positively correlated with BMI ($P < 0.0001$).

5. **Kaplan SL et al., (27)** from University of California, Sanfrancisco studied a total 205 children with true precocious puberty and evaluated them to find out the etiology. 81% (166) were female

children, out of which 59% (121) had idiopathic precocious puberty and 22% (45) had neurogenic cause. 9% (39) were boys, out of which 6.34% (13) had idiopathic precocious puberty and 12.68% (26) neurogenic.

6. **Paul Kaplowitz (28)** from Department of Endocrinology, Children's National Medical Center, Washington, D.C. reviewed data of 104 children referred for signs of early puberty. Criteria were developed to assign patients to one of seven diagnostic categories based on age, growth, and clinical findings and differences from the population mean for height and percentage of ideal body weight in the different groups were determined. Most of the patients referred (87%) were female, and the two most common diagnoses made were premature adrenarche (46%) and premature thelarche (18%). Only 9% (all girls) were thought to have true precocious puberty. Two conditions not well described in the literature, pubic hair of infancy and premature menses, were found in 8% and 5%, respectively. Patients with premature adrenarche were significantly taller and more overweight than the general population; a subgroup had evidence of accelerated growth and bone maturation but no worrisome endocrine findings. Acanthosis nigricans was found in 13% of the girls in this study, but the incidence of true endocrine pathology was very low. The majority of children being referred for precocious puberty have benign normal variants, with a very low incidence of endocrine pathology. Most girls presenting with minimal breast or pubic hair

development and normal growth velocity may be managed with observation and without a full endocrine evaluation.

7. **Rohani et al., (29)** from Endocrine Research Centre, Institute of Endocrinology and Metabolism (Hemmat Campus), in their case series study evaluated, 44 girls and 8 boys with precocious puberty in a 10 years period of time.

Mean age of girls and boys was 7.43±1.4 years and 5.8±2.1 years respectively. Most of the patients fell within the age category of 7-7.9 years old (40.9% for girls and 50% for boys). Patients, concerning etiology of precocious puberty were classified in three categories: 42.6% of patients had central precocious puberty (CPP), including idiopathic CPP (87.5%) and neurogenic CPP (12.5%). 23.3% of patients had peripheral precocious puberty (PPP), including congenital adrenal hyperplasia (CAH) (42.8%), ovarian cysts (28.4%), McCune-Albright syndrome (14.2%) and adrenal carcinoma (14.2%). 34.1% of girls and 25% of boys had normal variant puberty including premature thelarche (57%), premature adrenarche (38%) as well as premature menarche (4.7%).

The most common etiology of precocious puberty in girls was idiopathic central precocious puberty and premature thelarche, while in boys they were neurogenic central precocious puberty and CAH. Therefore precocious puberty in girls is usually benign. In boys, CNS

anomalies should first be considered in the differential diagnosis of CPP. Therefore brain Magnetic Resonance Imaging (MRI) is mandatory in all cases.

8. **A. Bajpai et al., (30)** from All India Institute of Medical Sciences, New Delhi, India evaluated records of 140 patients (114 girls, 26 boys) with precocious puberty. Girls outnumbered boys in this series (4.4:1). Neurogenic central isosexual precocious puberty (CIPP) was more common in boys (10out of 18, 55.6%) than girls (16 out of 77, 20.8%). The most common cause of neurogenic CIPP was hypothalamic hamartoma present in five girls and four boys. Other causes of neurogenic CIPP included neurotuberculosis, pituitary adenoma, hydrocephalus, post radiotherapy, CNS tumors and malformations. Peripheral precocious puberty (PPP) was secondary to adrenal causes in boys and ovarian cysts in girls. Benign variants of precocious puberty, such as premature thelarche and premature adrenarche, were present in 23 and six girls, respectively. Hypothyroidism was present in four girls and McCune-Albright syndrome in one girl. Girls with neurogenic CIPP had a lower age of onset as compared to idiopathic CIPP (3.6 ± 2.7 years vs 5.4 ± 2.5 years, (ρ = 0.014). The lowest age of onset was seen in girls with hypothalamic hamartoma (1.6 ± 0.9 years). Forty-seven girls with CIPP (seven neurogenic and 40 idiopathic) presented after the age of 6 years. Features of CNS involvement, in the form of seizures, mental retardation, raised intracranial tension or focal neurological deficits were present in

seven girls (43.8%) and four boys (40%), and gelastic seizures were present in three children. Girls with CIPP had greater bone age advancement (3.4 ± 1.5 years) and negative height standard deviation for bone age (-2.7 ± 1.5) than those with PPP (1.9 ± 1.6 years and -1.3 ± 1.3) and premature thelarche (0.4 ± 0.4 years and -0.8 ± 0.8). Patients with neurogenic CIPP had significantly higher levels of baseline and GnRHstimulated levels of LH and FSH and LH: FSH ratio than those with idiopathic CIPP. Occurrence of neurogenic CIPP in seven girls with an age of onset after 6 years emphasizes the need for CNS imaging in these girls contrary to the current recommendations. The fact that 65.6% cases of idiopathic CIPP presented after the age of 6 years raises the possibility that these patients may be physiological variants of normal puberty. Pointers to neurogenic CIPP included early age of onset in girls, clinical features of CNS involvement, and elevated basal and stimulated LH levels and LH: FSH ratio.

9. **Martin Chalumeau et al., (31)** from university pediatric hospital in Paris, France conducted a retrospective cohort study of all girls younger than 8 years with breast development related to CPP, seen between 1982 and 2000. For a pilot population (186 idiopathic, 11 revealing CNS abnormalities), the accuracy of the Lawson Wilkins Pediatric Endocrine Society recommendations were evaluated. Potential clinical, radiological, and biological predictors of CNS abnormalities were assessed by univariate and multivariate analyses. Applying the

Lawson Wilkins Pediatric Endocrine Society recommendations, 2 of 11 girls with CPP that revealed CNS abnormalities would not have been considered to require brain imaging. Independent predictors of CNS abnormalities were age at onset of puberty <6 years (adjusted odds ratio [AOR]: 6.7; 95% confidence interval [CI]: 1.5–29), lack of pubic hair at diagnosis (AOR: 7.7; 95% CI: 1.8 –33), and estradiol >110 pmol/L (AOR: 4.1, 95% CI: 1.0 –17). The identification of girls who have CPP and require cerebral imaging seems possible on the basis of validated, simple, and reproducible predictors: age and estradiol.

10. **B.M.Taher et al., (32)** from endocrine clinic of Jordan university hospital evaluated 43 girls and 7 boys with precocious puberty. Mean age for the girls with precocious puberty was 4.1 ± 2.5 S.D and for boys was 2.4 ± 1.9 S.D. among the girls 21% presented with breast development only,9% with pubic hair appearance and enlarged genitalia. Organic causes for precocious puberty were detected in 42% of girls and in all the boys. Idiopathic precocious puberty was more common among girls presenting with breast development only (89%) compared with those presenting with multiple signs (50%) and also was more common among girls presenting between 6 and 8 years of age(82%) than among those presenting <6 years of age (42%). Congenital adrenal hyperplasia was diagnosed in four boys and four girls. Hypothyroidism was diagnosed in three girls.

STUDY JUSTIFICATION

The advent of newer imaging modalities has led to the identification of neurological etiology in a majority of children previously diagnosed as having idiopathic central precocious puberty (33).

Clinicians who deal with CPP have two main concerns: detection of CNS abnormalities and short final height. Thus a means of identifying the group of girls who have CPP and are at high risk of CNS abnormalities is essential.

Though there are many reports regarding the sexual precocity from west, Indian data regarding precocious puberty are limited (23, 24, 25, and 30).

This study was planned to evaluate the etiology, clinical features, and endocrine profile and factors predicting neurogenic etiology in children with central precocious puberty (CPP) being followed up in a tertiary care center.

AIM OF THE STUDY

1. To evaluate the clinical and endocrine profile of patients with precocious puberty followed up in a tertiary care hospital

2. To identify predictors of central precocious puberty (CPP) that reveals central nervous system (CNS) abnormalities in girls with CPP.

MATERLALS AND METHODS

METHODOLOGY

STUDY DESIGN :

Descriptive Study

STUDY SETTING :

Endocrinology Division, ICH and HC, Egmore.

STUDY PERIOD :

October 2009 to September 2011.

STUDY POPULATION :

All cases attending endocrinology out-patient and diagnosed as premature sexual development.

CASE DEFINITION :

Appearance of secondary sexual characteristics in an age that is less 8 years in girls and 9 years in boys or the onset of menstruation Before 9.5 years in girls.

MANOEUVRE:

This study was done in the endocrinology outpatient department of Institute of child health Egmore. Retrospective analysis of case records of children with precocious puberty under follow up during the study period

and prospective analysis over a period of 3 years, seventy seven children were enrolled in the study through non-probability convenience sampling method. Analysis included age of onset, family history, presenting features of precocity, features suggestive of central nervous system (CNS) involvement, exposure to drugs especially steroids, and features of endocrinopathies including hypothyroidism and congenital adrenal hyperplasia (CAH). The age at the onset of puberty was defined as the age when breast development was first noted by the patient or their parents. Other data were the values recorded at the first physical examination.

Clinical features, such as the stage of pubertal development, CNS abnormalities and features of endocrine disorders, were analyzed. Testicular volume was measured by a Praders orchidometer. Sexual maturity was rated according to Tanner's pubertal staging in both boys and girls.

Height was measured with a Harpenden stadiometer and weight was recorded using a digital weighing scale and compared with Agarwal standard charts, for age and sex matched percentiles (47, 48) and were expressed as Z score with respect to chronological age and sex. Body weight was expressed as body mass index (BMI) (weight in kilograms/height in m^2)

Endocrine evaluation included baseline luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone/estrogen levels in all patients. A gonadotropin releasing hormone agonist (GnRH agonist) stimulation test was performed in doubtful cases where basal gonadotropin levels are inconclusive. LH and FSH levels were estimated at 0 hour, 4 hour and 24 hour after injection of 10 μg /kg of GnRH agonist intramuscularly (3). Precocious puberty was diagnosed with pubertal levels of LH or a ratio of LH: FSH greater than 1, Stimulated LH > 10mIu /mL, and LH rises three fold over baseline. Blunted response is pathognomonic of peripheral precocious puberty. Other endocrine investigations included thyroid profile, 17-hydroxyprogesterone (170HP) (baseline and after adrenocorticotropic hormone [ACTH] stimulation), dehydroepiandrosterone (DHEA) and human chorionic gonadotropin (HCG) estimations. All hormonal investigations were carried out by enzyme immunoassay method. Bone age (BA) was estimated using the radiographic atlas of skeletal development. Ultrasonogram (USG) of the abdomen and pelvis was performed in all girls with precocious puberty and computerized tomography (CT) scan and Magnetic resonance imaging (MRI) of the brain was performed in children as and when indicated.

STATISTICAL ANALYSIS

Datas were entered using Microsoft corp. excel and analysed using SPSS (statistical package for social sciences) version 16 for windows. Statistical analysis included estimation of mean and standard deviation for clinical auxological and endocrine parameters. Differences between two continuous variables were estimated by independent t-test. P values less than 0.05 were considered significant.

OBSERVATIONS

Out of 77 children with precocious puberty, 76.6% (n=59) were girls and 23.4 %(n=18) were boys (figure 1).

AGE OF ONSET

Mean age of onset for girls and boys under the study were 5.8 ± 2.1 and 7.43 ± 1.4 respectively. Majority of the children in the study population were in the age category of 6-7years (48% girls and 52% boys). Age of onset was similar in girls and boys with CPP and PPP (Table 2 and 3). Girls with neurogenic CPP had earlier age of onset than those with idiopathic CPP, while the difference in boys was not significant (Table 5). Two girls with hypothalamic hamartoma had the lowest age of onset 2 years and 2.6 years respectively. Girls with premature thelarche had a relatively later age of onset compared to those with CPP (Table 6).

CLINICAL FEATURES

Breast enlargement was the commonest presenting feature in 81.4% girls (n=48) and cyclical vaginal bleeding was the presenting complaint in 18.6% girls (n=11). Appearance of pubic hair was present in all girls with peripheral precocity 5.1% (n=3) and in 71.8% of girls

(n=28) with central precocious puberty. Family history of early menarche was present in 8.5% girls (n=5) and all of them presented with idiopathic CPP. All boys with central precocity (n=13) had testicular and penile enlargement while pubarche was present in 27% (n=5).Testicular volume was prepubertal in all the 4 boys with non- classical 21 hydroxylase deficiency. Involvement of central nervous system like seizures and mental retardation, was present in 28.5% girls (n=2) and 28.5 % boys (n=2) with neurogenic CPP.

Table : 2 Comparison of central and peripheral precocious puberty in boys

No	Clinical and auxological parameters	CPP (mean±S.D)	PPP (mean±S.D)	T Value	P Value
1.	Number	13	5	-	-
2.	Age of onset (yr)	5.6± 0.9	7.3 ±0.5	3.264	0.005
3.	Height SD	1.9±0.2	1.4±0.2	3.643	0.002
4.	Bone age-chronological age(yr)	4.1±1.1	3.3± 0.6	1.491	0.080

Table : 3 Comparison of central and peripheral precocious puberty in girls

No.	Clinical and auxological parameters	CPP (mean±S.D)	PPP (mean±S.D)	T Value	P Value
1.	Number	39	3	-	-
2.	Age of onset (yr)	5.8 ± 0.8	6.2 ±0.8	0.735	0.467
3.	Height SD	1.7±0.3	1.3±0.1	2.106	0.042
4.	Bone age-chronological age(yr)	3.4±0.8	3.1± 0.5	0.620	0.538

Auxological parameters:

10 out of 14 children with neurogenic CPP had a height above the 97th centile, and in the rest of the 4 children it was between the 75th and 97th centile. Height was measured in 38 children with idiopathic CPP, of which 24 children fell between the 75th and 97th centile and 14 children were above the 97th centile. The height of 15 girls with premature thelarche fell between the 3rd and 25th centile, and in 8 girls with PPP height was between the 25th and 50th centile. In 2 girls with hypothyroidism height was less than 3rd centile.

In 25 girls with CPP, BMI was more than 85th centile (overweight), in 7 girls with CPP and 2 girls with hypothyroidism BMI was above the 95th centile (obesity). In 7 girls with CPP and in 3 girls with PPP, BMI was between the 75th and 85th centile.

In 13 boys with CPP, BMI was between the 10 and 25th centile and in 3 boys with CPP and 5 boys with PPP, BMI was between the 25th and 50th centile.

42.5% Girls with precocious puberty were overweight (n=25) and 15.2% (n=9) were obese, unlike the boys who were neither overweight nor obese.

BONE AGE EVALUATION

Bone age was advanced in all children with precocious puberty except in 2 girls in whom hypothyroidism was the underlying aetiology. They presented with a markedly retarded bone age (Bone age – chronological age = -2). Advanced bone age was most pronounced among all 4 boys with non-classical 21 hydroxylase deficiency. Boys with central precocity had greater bone age advancement compared to boys with peripheral precocity (Table 2). No significant difference in bone age advancement was seen in girls with central precocity compared with peripheral precocity (table 3). However advanced bone age was statistically significant in boys and girls with idiopathic CPP compared with neurogenic CPP (table 4 and 5).

Table : 4 Comparison of idiopathic and neurogenic precocious puberty in boys

No	Clinical and endocrine profile	Idiopathic CPP (Mean±S.D)	Neurogenic CPP (Mean±S.D)	T-value	P-value
1.	Number	6	7	-	-
2	Age of onset (yr)	5.7±0.9	5.6±1.0	0.242	0.813
3	Height S.D	2.0±0.1	1.7±0.09	4.228	0.001
4	BA-CA (yr)	3.1±0.4	5.0±0.6	6.566	<0.001
5	Serum. Testosterone (ng/dL)	39.8±8.1	39.6±7.3	0.923	0.968
6	Basal LH(mIu/ml)	3.9±0.7	5.0±0.7	2.682	0.021
7	Basal FSH(mIu/ml)	2.6±0.2	3.5±0.6	3.214	0.008
8	Basal LH: FSH	1.5±0.4	1.4±0.1	0.539	0.600
9	Peak LH(mIu/ml)	27.7±2.8	42.3±3.6	7.897	<0.001
10	Peak FSH(mIu/ml)	14.5±1.0	13.2±1.5	1.736	0.110
11	Peak LH: FSH	1.9±0.1	3.2±0.4	6.554	<0.001

ENDOCRINE INVESTIGATIONS

Thyroid function test was done in all the 77 children enrolled in the study. Elevated TSH (>5 μIU/ml) and decreased T4 (<51 nmol/L) was observed in 3.4% girls (n=2). Girls with neurogenic CPP had higher levels of baseline LH, FSH and LH: FSH ratio than those with idiopathic CPP (table 5). The difference was accentuated by GnRH stimulation. Boys with neurogenic CPP had higher levels of baseline LH, FSH, peak LH and peak LH: FSH ratio compared to those with idiopathic CPP (table 4). Predominant FSH response was seen in all girls diagnosed as isolated premature thelarche. Though basal FSH was indiscriminatory between premature thelarche and central precocious puberty, a significant difference was observed in FSH response after GnRH stimulation (table 6).

Table : 5 Comparison of idiopathic and neurogenic precocious puberty in girls

no	Clinical and endocrine profile	Idiopathic CPP (Mean±S.D)	Neurogenic CPP (Mean±S.D)	T-value	P-value
1.	Number	32	7	-	-
2	Age of onset (yr)	6.0±0.7	4.8±0.3	4.476	<0.001
3	Height S.D	1.6±0.2	1.9±0.2	2.616	0.013
4	BA-CA (yr)	3.1±0.7	4.5±0.4	5.016	<0.001
5	Serum. Estradiol (pg/mL)	6.6±0.9	13.3±1.0	16.471	<0.001
6	Basal LH(mIu/ml)	3.9±0.6	5.4±0.6	5.634	<0.001
7	Basal FSH(mIu/ml)	2.7±0.3	4.3±0.6	6.357	<0.001
8	Basal LH: FSH	1.4±0.2	1.2±0.1	1.859	0.071
9	Peak LH(mIu/ml)	32.6±5.1	42.1±6.9	4.188	<0.001
10	Peak FSH(mIu/ml)	14.67±1.01	14.9±2.5	0.244	0.815
11	Peak LH: FSH	2.2±0.3	2.5±0.3	1.813	0.078

Serum 17 β estradiol estimation was done in all 59 girls with precocious puberty. Elevated estradiol levels (> 10 pg / mL) were seen in

all 39 girls with central precocity. Significant elevation was seen in girls with neurogenic CPP compared with idiopathic CPP and premature thelarche (table5, 6).

Table : 6 Comparison of central precocious puberty and premature thelarche in girls

No	Clinical and endocrine profile	CPP (Mean±S.D)	Premature thelarche (Mean±S.D)	T-value	P-value
1.	Number	39	15	-	-
2	Age of onset (yr)	5.8±0.8	7.0±0.2	8.466	<0.001
3	Height S.D	1.7±0.3	0.7±0.2	10.931	<0.001
4	BA-CA (yr)	3.4±0.8	0.5±0.4	11.949	<0.001
5	Serum estradiol (pg/mL)	7.8±2.7	5.5±1.6	2.984	0.004
6	Basal LH(mIu/ml)	4.2±0.8	1.8±0.4	13.283	<0.001
7	Basal FSH(mIu/ml)	2.9±0.7	3.0±0.5	0.114	0.910
8	Basal LH: FSH	1.4±0.2	0.6±0.1	10.948	<0.001
9	Peak LH(mIu/ml)	34.3±6.5	3.8±0.6	28.901	<0.001
10	Peak FSH(mIu/ml)	14.7±1.3	7.8±0.4	28.000	0.001
11	Peak LH: FSH	2.2±0.3	0.4±0.07	27.317	<0.001

Serum testosterone levels were estimated in all the 18 boys with premature sexual development. Levels more than 25 ng /dL was present in all 13 boys with central precocity. No significant difference in serum testosterone levels was observed in boys with idiopathic and neurogenic CPP (table 4). A grossly elevated serum testosterone level (410 ng /dL) was present in 1 boy with testotoxicosis.

ULTRASONOGRAM OF PELVIS

Ultrasonogram (USG) of pelvis for utero-ovarian evaluation demonstrated enlarged uterus (> 3.5 cm) and ovaries in 66% of the girls (n=39) (All the 39 girls were diagnosed as CPP). 27% of the girls (n=16) with central precocity had multiple small ovarian cysts. Endometrial thickness of more than 3mm was present in 87% of the girls (n=34) with central precocity.

NEUROIMAGING

CT brain was done in 10 girls and 6 boys with central precocity. Craniopharyngioma was detected in 1 girl. MRI brain was done in 29 girls and 7 boys. Neurotuberculosis in 5.1% girls (n=2), empty sella in 5.1% girls (n=2) and hypothalamic hamartoma in 5.1% girls (n=2) were the findings revealed by MRI in girls with central precocious puberty. Supracellar arachnoid cyst in 15.3% boys (n=2), hypothalamic

hamartoma in 23% boys (n=3) and neurotuberculosis in 15.3% boys (n=2) were the abnormalities detected by MRI in boys with central etiology. Neuroimaging revealed abnormalities in 11.9% girls (n=7) and 38.9% boys (n=7).

PREDICTORS OF NEUROGENIC ETIOLOGY IN CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY :

No significant difference in age of onset was observed between boys with idiopathic and neurogenic CPP.

Advanced bone age, elevated basal LH, basal FSH, Peak LH and Peak LH : FSH ratio were significantly higher in boys with neurogenic CPP (Table 4).

Compared to idiopathic CPP, girls with neurogenic CPP had an earlier age of onset, advanced bone age and height S.P. scores (Table 5).

Elevated serum estradiol, basal LH, basal FSH, Peak LH were significantly higher in girls with neurogenic CPP (Table 5).

Table : 7 Etiology of precocious puberty

No.	Category		Girls	Boys	Total
1.	Idiopathic central precocity		32 (54.2%)	6 (33.3%)	38 (49.4%)
2.	Neurogenic central precocity		7 (11.9%)	7 (38.9%)	14 (18.2%)
	a.	Neurotuberculosis	2	2	
	b.	Hypothalamic hamartoma	2	3	
	c.	Craniopharyngioma	1	-	
	d.	Empty sella syndrome	2	-	
	e.	Supracellar arachnoid cyst	-	2	
3.	Premature thelarche		15(25.4%)	-	15(19.5%)
4.	Peripheral precocity		3(5.1%)	5(27.8%)	8(10.4%)
	a.	Ovarian cyst	2	-	
	b.	McCune-Albright syndrome	1	-	
	c.	Non-classical 21 hydroxylase deficiency	-	4	
	d.	Male-limited precocious puberty (Testotoxicosis)	-	1	
5.	Hypothyroidism		2(3.4%)		2(2.6%)

DIAGNOSIS

Based on clinical and endocrine evaluation the study population was categorized into three major groups (table 7) (i) Central precocious puberty (ii) Peripheral precocious puberty and (iii) Isolated normal variants.

The most common etiology among our study population (figure 2) was central precocious puberty seen in 66% girls (n=39) and 72.2% boys (n=13) respectively. Out of the above 33.3% boys (n=6) and 54.2% girls (n=32) were diagnosed with idiopathic central precocious puberty. 38.9% boys (n=7) and 11.9% girls (n=7) were diagnosed with neurogenic central precocious puberty.

Among the central causes (figure 3) neurotuberculosis was identified as the etiology in 11.1% boys (n=2) and in 3.3% girls (n=2). Hypothalamic hamartoma in 16.6% boys (n=3) and 3.3% girls (n=2) were the cause for central precocity. In 11.1% boys (n=2) arachnoid cyst was identified as the etiology and empty sella was the etiology in 3.3% girls (n=2).

Hypothyroidism was present in 3.4% girls (n=2) and isolated premature thelarche in 25.4% girls (n=15). No child with isolated

premature pubarche or premature menarche has been reported in our study.

Peripheral precocious puberty (figure 4) was identified as the etiology in 27.8% boys (n=5) and 5.1% girls (n=3). Among the peripheral causes in girls ovarian cyst in 3.3% (n=2) and McCune-Albright syndrome in 1.7% (n=1) were identified as the etiology. Among boys non-classical 21 hydroxylase deficiency was present in 22.2% (n=4) and testotoxicosis in 5.5% (n=1).

Figure 1 : Sex distribution of study population

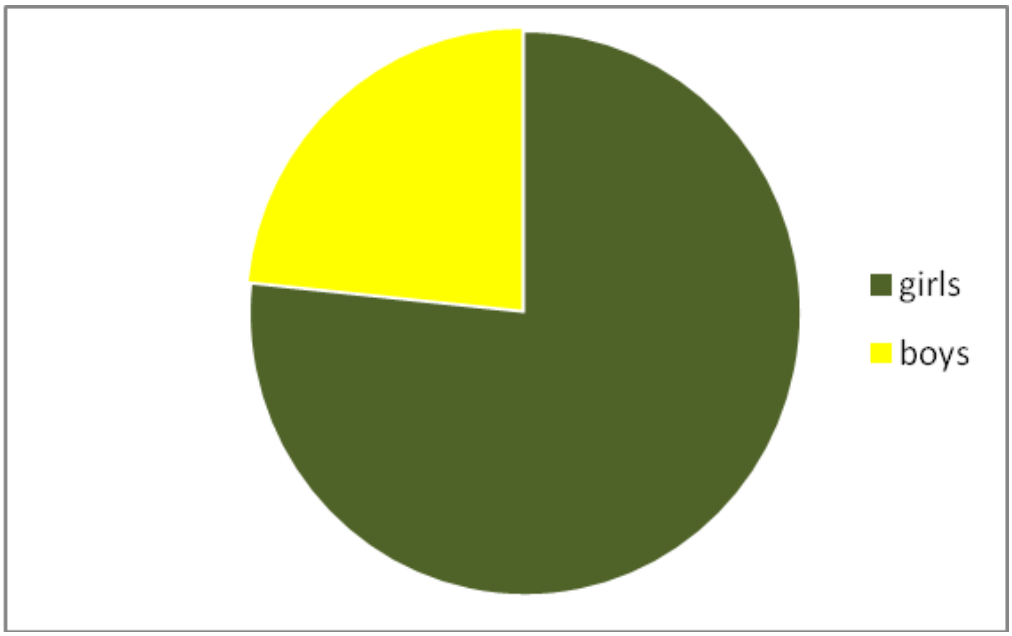


Fig 2: Etiology of precocious puberty

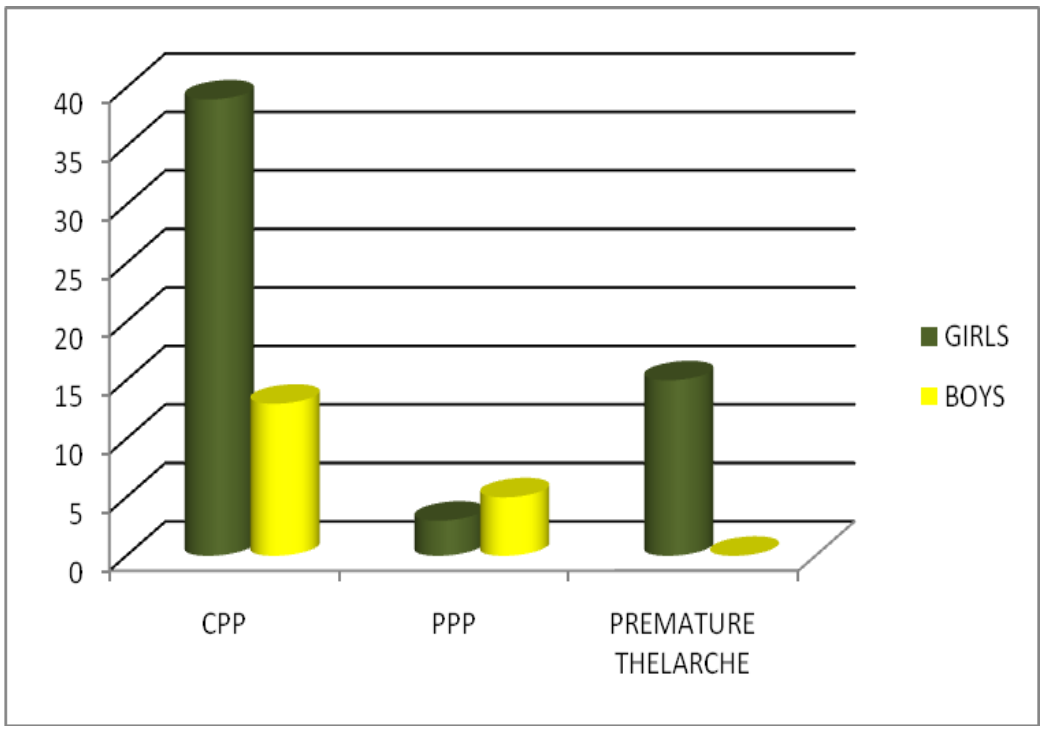


Fig 3: Etiology of neurogenic central precocious puberty

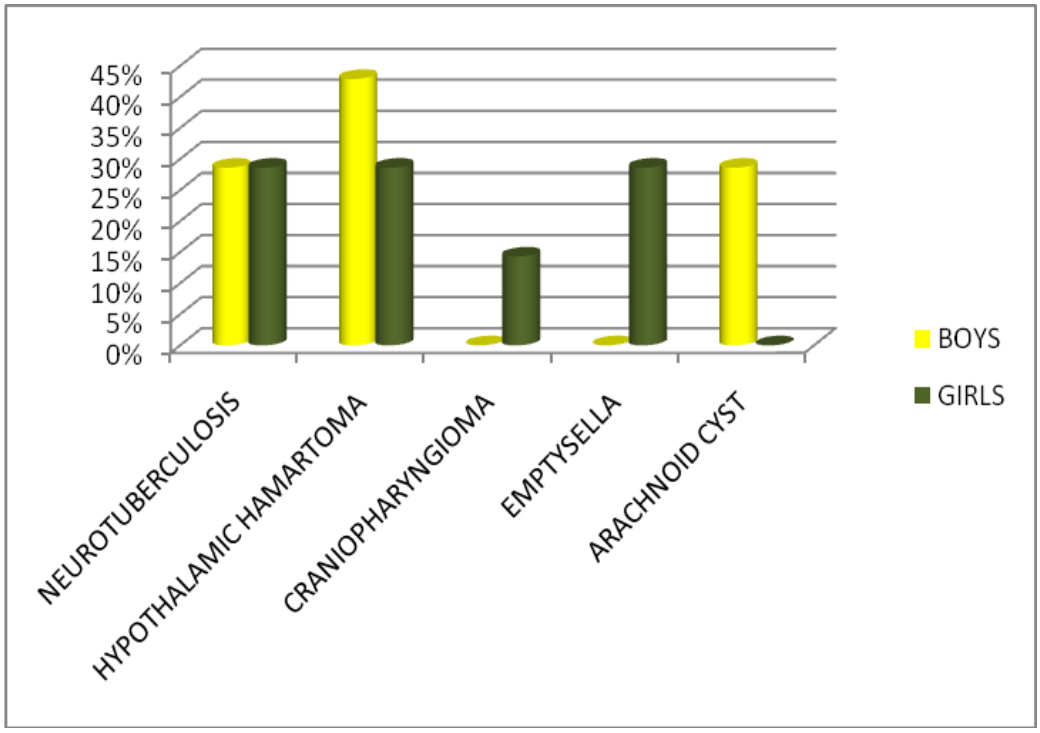
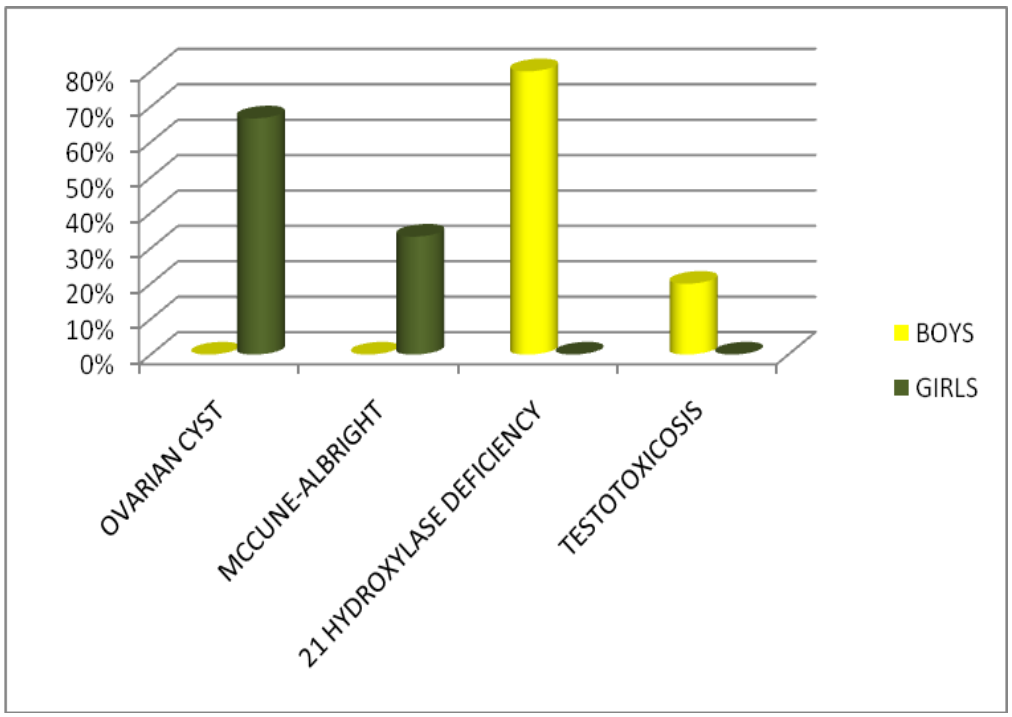


Fig 4: Etiology of peripheral precocious puberty



DISCUSSION

Wide variation exists in the clinical spectrum of premature sexual developments and its etiology is multifactorial. Precocious puberty is present more commonly in girls than boys (female to male ratio 5-10:1 approximately). (23-32) In our study 77% of children were girls and 23% were boys, therefore female to male ratio was 3.5:1. In studies by Meena Desai et al (23), Bajpai et al (30), Chemaitilly et al (26), and Taher et al (32), 72.5%, 81%, 89%, 85% and 86 %, of patients were girls respectively.

Our data demonstrate that central precocious puberty was present more commonly in girls, seen in 51% (39 / 77) than boys 17% (13/77). The majority of girls with central precocious puberty (82 %) had idiopathic CPP where no etiology has been established (idiopathic CPP to neurogenic CPP ratio, 5:1), whereas a neurogenic cause was identified in 54% of boys (idiopathic CPP to neurogenic CPP ratio, 1:1). This further signifies the fact that CPP is uncommon in boys, but when it does occur it is usually due to an underlying neurological cause (39). The incidence of neurogenic CPP in the present study 18 % is comparable to that of other reports from our country (23, 25 and 30). This increased incidence of neurogenic CPP compared to studies done earlier may be due to an improvement in radiological investigations (24, 40). Recent studies have shown an increase in the incidence of neurogenic CPP (29, 30). Our

findings were consistent with Bajpai et al, where 67.5% of female patients had CPP, 80% of which were idiopathic CPP. Furthermore, 56% of boys with CPP had neurogenic cause and 44 % had Idiopathic CPP. Findings of the most studies reiterate the increased incidence of idiopathic central precocious puberty in girls and neurogenic central precocious puberty in boys. The etiology of idiopathic precocious puberty in girls is unknown. This is possibly explained by early reactivation of hypothalamic-pituitary- gonadal axis in girls in comparison to boys (41).

Hypothalamic hamartoma was the commonest cause of neurogenic CPP (35.7%, 5/14) in our study (three girls and two boys). Gelastic seizures or laughing spells is the commonest presentation; none of our children with hypothalamic hamartoma manifested it. LH-releasing hormone containing fibers have been observed within hamartoma tissues in patients with CPP. These patients presented at an early age, as in other reports (42). These patients respond to GnRH analog therapy and surgical correction is not required (42, 43). Neurotuberculosis was the second most common cause of neurogenic CPP in this series, reflecting a greater prevalence of tuberculosis in our country. We report two girls who had all the manifestations of central precocious puberty but empty sella was the only finding on MRI brain. Empty sella syndrome in association with CPP has been reported (44), but whether it plays a role in causing CPP is debatable. Supracellar arachnoid cyst was reported in two boys with

features of central precocious puberty and headache was the only presenting complaint.

According to the present study, in 5.1% of girls and 27.8% of boys peripheral causes were identified as the etiology of precocious puberty. Adrenal causes, Non-classic 21-hydroxylase deficiency are the commonest cause (80%, 4/5) of PPP in boys, as reported by Desai et al (23), Taher et al (32), and Bajpai et al (30). These boys presents with enlarged penis and early appearance of pubic hair with prepubertal testes in the absence of salt wasting. 170HP levels are elevated and an ACTH stimulation test is required for definitive diagnosis. One boy presented with all the features of central precocious puberty with grossly elevated basal testosterone. However response to GnRH stimulation is prepubertal and testicular biopsy revealed leydig cell hyperplasia confirming testotoxicosis.

PPP in girls is usually secondary to follicular ovarian cysts. Follicular cysts secrete estrogens that cause mammary development or even non-cyclical vaginal bleeding. They can be recurrent, causing a transient rise of estradiol levels. Larger follicular cysts can present torsion of the pedicle and infarction, requiring surgical intervention. Girls with CPP may have multiple ovarian cysts on USG, as in most post pubertal girls. These should not be confused with estrogenic ovarian cysts. The cysts resolve spontaneously in most patients as the puberty regresses (45).

Clinical diagnosis of McCune-Albright syndrome was diagnosed in one girl with typical café au lait macules, polyostotic fibrous dysplasia and GnRH- independent precocious puberty. She had elevated estradiol, multicystic ovaries on USG of pelvis with low basal LH & pre-pubertal response to GnRH stimulation.

Long-standing untreated primary hypothyroidism has been associated with precocious puberty. This is explained by an increase in the levels of prolactin and FSH and FSH-like activity of the alpha subunit of TSH (46). Two girls present with delayed bone age, clinical features of hypothyroidism, significantly elevated TSH (>100 mIu/mL), normal gonadotropin levels and elevated estradiol levels. Thyroxine supplementation in these girls leads to normalization of thyroid status and disappearance of secondary sexual characteristics.

In our study incomplete variant was considered as the second common cause (25.4%) of precocious puberty in girls, with dominancy of premature thelarche. None of the children were reported with premature pubarche in this series. Desai et al (23) study showed 46 % of girls with precocious puberty had normal variant and 35 % of them had premature thelarche. In comparable with our finding, supported by the conclusions of Taher et al (32) and Bajpai et al (30) studies, incomplete normal

variant was the cause of precocious puberty in 21% and 25.5% of patients respectively.

Girls with neurogenic CPP had an earlier age of onset than those with idiopathic CPP, a finding that is similar to that in other studies (23, 39, and 40). In boys, the age of onset of neurogenic CPP was not different from that of idiopathic CPP. This emphasizes the need for careful CNS imaging in boys with precocious puberty. Current guidelines recommend that CNS imaging is not required in girls after 6 years as the incidence of neurogenic CPP is very low after this age (18). Studies have, however, indicated that neurogenic etiology may be present in girls with pubertal onset between 6 and 8 years of age

The LWPES's recommendations (12) were formulated to identify girls who have CPP and need evaluation for risk of both CNS abnormalities and short final height. Their conclusions were derived mainly from a study in which the cause of precocious puberty was not assessed. Those new recommendations raised some concerns. Given that they were designed to apply to American girls, we found that in the present study, three girls older than 6 years had neurogenic CPP. In a multicentric Italian study, 16% of girls older than 7 years with precocious puberty had neurogenic CPP (13) .These findings indicate the need for

CNS imaging in these girls in contrast to the current recommendations. The need for CNS imaging should therefore be individualized according to the age at onset, rate of progression and neurological features. Larger studies may be required to revise these guidelines.

14 girls with idiopathic CPP (14 /32, 44%) presented after the age of 6 years. This, coupled with recent findings that puberty is occurring earlier in girls, raises the question whether the current age criteria for the diagnosis of precocious puberty are inappropriately high. The present study was conducted in a tertiary referral center and thus has the limitation of selection bias in regard to physiological variation, which is less likely to be referred. Recommendations for lowering the age limit for the definition of precocious puberty have been made but have not yet been universally accepted (12). These recommendations are based on western studies and do not take into account factors such as nutrition, obesity and socio-economic status. Age criteria for precocious puberty in developing countries require population-based studies that are so far scanty.

Features of CNS involvement, such as seizures, mental retardation, hydrocephalus and focal neurological deficits, favor neurogenic CPP. Patients with neurogenic CPP have advanced bone age which is also the

case in the present study early age of onset. Levels of estradiol, basal LH, basal FSH and Peak LH were higher in neurogenic CPP compared to idiopathic CPP in girls. Our findings were comparable with Cacciari et al (35) and Bajpai et al (30), where early age of onset in girls, clinical features of CNS involvement, and elevated basal and stimulated LH,FSH levels and LH: FSH ratio were the predictors of neurogenic CPP. However study by Martin chalumeau et al (31), revealed entirely different predictors like, age at onset of puberty less than 6 years, lack of pubic hair at diagnosis, and estradiol more than 110 pmol/L. This can be explained by difference in statistical analysis, selection bias and number of children recruited for the study.

CONCLUSION

1. Precocious puberty was more common among girls. The most common etiology of precocious puberty in girls was idiopathic CPP (54.2%) followed by premature thelarche (25.4%).

2. Most common etiology of precocious puberty in boys was neurogenic CPP (38.9%) followed by peripheral precocious puberty due to CAH, non – classical 21hydroxylase deficiency (23%).

3. Central precocious puberty in girls is usually idiopathic, but in boys is more likely to be the result of a demonstrable CNS lesion. This conclusion made it mandatory for neuro imaging (either CT or MRI) in boys with CPP.

4. Neurogenic CPP was present in three girls with age of onset after 6 years, indicating the need for CNS imaging in girls with age of onset after 6 years in contrary to the current recommendations.

5. Predictors of central nervous system abnormalities in girls with neurogenic CPP were early age of onset, advanced bone age, elevated levels of serum estradiol, basal LH, basal FSH and Peak LH..

SUMMARY

1. All children presenting with precocious puberty require a detailed history and clinical evaluation before commencing investigations and treatment.

2. Normal pubertal variants like premature thelarche require only reassurance and periodic follow-up. The pediatrician therefore should be adept in differentiating normal pubertal variants from pathological precocious puberty.

3. Unnecessary investigations should be avoided if features of precocious puberty are inconsistent or not clearly evident and the patient must be reviewed after a few months for reassessment.

4. All forms of PPP should be managed according to the etiology, predicted adult height and psychological concerns.

5. Suppression of CPP with GnRH analogues should be considered when there is significant compromise to adult stature and behavioral issues.

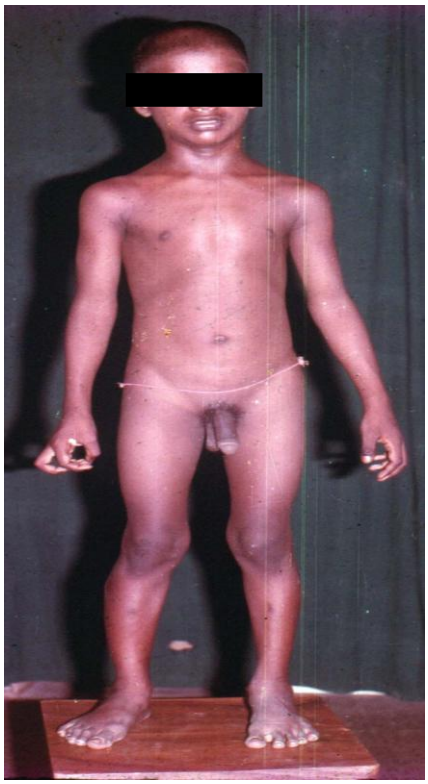
6. Urgent need for population-based studies including biological work-up and brain imaging to exclude premature thelarche, primary gonadal precocious puberty, and CPP revealing CNS abnormalities.

7. Predictors for short final height and/or CNS abnormalities, identified by rigorous statistical analysis, need to be established.

4 yr old girl with McCune – Albright syndrome

3 yr old girl with empty sella syndrome presenting as neurogenic CPP

5 yr old boy with testotoxicosis presenting as Peripheral precocity



4 yr old with idiopathic CPP

6 yr old girl with hypothyroidism and precocious puberty

3 yr old girl with supracellar arachnoid cyst presenting as neurogenic CPP

4 yr old girl with craniopharyngioma presenting as neurogenic CPP

2.5 yr old girl with hypothalamic hamartoma presenting as neurogenic CPP

ANNEXURE 1

PROFORMA

Serial No

Name :

Age:

Sex

Address :

Age of onset of Presenting Complaints :

Presenting Complaints :

Past history of CNS involvement :

H/O drug intake (exogenous steroids) :

Family history of early menarche :

CLINICAL EXAMINATION

Goiter :

Features of hypothyroidism :

Axillary Hair :

Breast Development (Tanner Staging) :

Galactorrhea :

Pubic Hair (Tanner Staging) :

Clitoromegaly :

Stretch penile length (cm) :

Testicular Volume (Tanner Staging) :

Menstruation :

ANTHRAPOMETRY

Weight :

Height :

BMI :

INVESTIGATIONS

RADIOLOGICAL

X-ray for Bone Age :

USG Abdomen :

Pelvis :

C.T. Scan Brain :

MRI Brain :

HORMONAL (BLOOD)

T_4 :

TSH :

GNRH STIMULATION	**BASAL**	**PEAK**
LH		
FSH		

17 β ESTRADIOL :

TESTOSTERONE :

17-OHP :

DHEA / DHEAS :

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